

	UPREGULATED	H:L Vpu <sup>+</sup> =H	L:H Vpu <sup>+</sup> =L	Mean	Description
Adhesion molecule	Chitinase-3-like protein 2 (CHI3L2)	2.315	1.710	2.013	Lectin molecule that is secreted from various cell types. High affinity binding to chitooligosaccharides and other glycans; does not bind heparin. Implicated in development, inflammatory disease and cancer.
GTPase enzyme	Dynamin-2	2.148	1.344	1.746	GTPase protein involved in budding and scission of vesicles from plasma membrane. Required for Nef-mediated infectivity enhancement.
Anti-oxidation enzyme	Thioredoxin-related transmembrane protein 2 (TMX)	1.856	1.224	1.540	Associated with human retrovirus pathology. Reduces oxidative stress.
Ion channel	Voltage-gated potassium channel subunit beta-2 (KCNAB2)	1.824	1.195	1.510	Voltage gated potassium channels are known to be dysregulated in HIV-associated dementia (HAD). Shown to be upregulated by HIV-1 gp120.
Pro-inflammatory enzyme	Prostaglandin E synthase 3 (PTGES3)	1.144	1.366	1.326	Membrane bound. Produces Prostaglandin E inflammatory lipids. siRNA knockdown reduce HIV production in culture. Shown to interact with Vpu in a mass spectrometry screening assay.
Anti-oxidation enzyme	Peroxiredoxin-2 (PRDX2)	1.300	1.315	1.308	Reduces oxidative stress. Might participate in signaling cascades by regulating cellular hydrogen peroxide levels. Known to be cleaved by HIV protease.
	DOWNREGULATED	H:L Vpu <sup>+</sup> =H	L:H Vpu <sup>+</sup> =L	Mean	Description
Restriction factor	BST2 (CD317; BST2)*	0.451	0.058	0.255	Type-II transmembrane protein that contains a second membrane anchor via a C-terminal GPI moiety. Forms coiled-coil homodimers. Prevents budding of HIV-1 virions from cell membrane. Induces NF- $\kappa$ B signaling. Induces inhibitory signals in pDCs via ILT7 interaction.
Immunoreceptor	Integrin associated protein (IAP; CD47)*	0.485	N/A	0.485	Transmembrane protein containing a N-terminal IgV immunoglobulin-like domain, five transmembrane domains, and a short cytosolic tail. Many different, context-dependent functions. Binds Sirp $\alpha$ on macrophages to inhibit phagocytosis. Binds thrombospondin. Can signal pro-apoptotic and/or activating stimuli.
Adhesion/Immunoreceptor	Leukosialin (SPN; CD43)*	0.716	0.613	0.665	Sialoglycoprotein abundantly expressed on the plasma membrane of human T cells, granulocytes, monocytes, and B cells. Important for immune function. May participate in T cell receptor activation. Localizes to uropod structures in T cells.
Adhesion molecule	Intercellular adhesion molecule 3 (ICAM-3; CD50)*	0.469	0.646	0.558	Transmembrane glycoprotein adhesion molecule containing five immunoglobulin-like C2-type domains. Binds to LFA-1, MAC-1, and DC-SIGN. Component of immunological synapse (IS) structures. Constitutively and abundantly expressed by all leukocytes and may be important for the initiation of cell-to-cell contacts. Functions not only as an adhesion molecule, but also as a potent signalling molecule.
	Intercellular adhesion molecule 2 (ICAM-2; CD102)*	0.395	0.814	0.605	Transmembrane glycoprotein adhesion molecule containing two immunoglobulin-like C2-type domains. Binds LFA-1. Expressed more highly on endothelial vesicles than leukocytes. Involved in leukocyte infiltration out of blood and IS formation. Less important for IS formation than ICAM-3 and ICAM-1.
	CD99 (MIC2)*	0.542	0.827	0.685	Surface adhesion molecule involved in leukocyte infiltration out of blood.
	Integrin alpha-4 ( $\alpha$ 4; CD49d)	0.569	0.876	0.723	Component of integrin heterodimers. Integrin $\alpha$ 4 $\beta$ 7 is a major gut homing marker. $\alpha$ 4 $\beta$ 7 binds gp120. Suggested as an alternative receptor for HIV-1 cell entry.
	Platelet endothelial cell adhesion molecule (PECAM-1; CD31).	0.681	0.876	0.779	Transmembrane protein containing six immunoglobulin-like C2-type domains. Adhesion molecule expressed on many leukocytes. Dominant component of endothelial cell intercellular junctions. Important for leukocyte migration, angiogenesis, and integrin activation. Marker of recent thymic immigrants.
Metabolite transporter	Monocarboxylate transporter 1 (MCT1; SLC16A1)	0.613	0.890	0.752	Monocarboxylate/H <sup>+</sup> bidirectional symport. Transports monocarboxylates such as lactate, pyruvate, acetate, and acetoacetate across the cell membrane. Binds CD147 at the cell surface for optimal activity.

**Table S1. List of putative candidates of Vpu-mediated downregulation from SILAC-based proteomic screen.**

H=heavy isotope signal, L=light isotope signal. \*Also detected as downregulated by HIV-1 in a second proteomics-based membrane protein screening study (26).